UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/146,783	09/03/1998	NICHOLAS JOHN DEACON	9606Z-IY	9825

7590 10/21/2003

SCULLY SCOTT MURPHY AND PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	25

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/146,783	DEACON ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,66,67,123 and 126-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,66,67,123 and 126-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

Status of the Claims

1. Applicants requested that previously withdrawn claims 137-152 be considered for examination in view of the telephonic conversation held on 18 March, 2003. Upon further reconsideration, these claims have been rejoined. Accordingly, claims 50, 66, 67, 123, and 126-152 are currently under examination.

35 U.S.C. § 112, Second Paragraph

2. The previous rejection of claim 50 under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for referencing immune responses in both humans and primates, is hereby withdrawn in response to applicants' amendment.

3. The previous rejection of claims 122, 124, 129, and 134 under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

35 U.S.C. § 112, First Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 49, 50, 66, 67, 85, 120-136, and 153-156 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods of vaccinating individuals against AIDS or AIDS related pathologies by administering vaccine compositions comprising a non-pathogenic HIV-1 isolate carrying deletions in the Nef/LTR coding regions. As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to demonstrate that other genotypically diverse Nef-deficient HIV-1 isolates will behave in the same manner across a genetically diverse group of people. The prior art teaches that many viral and host factors contribute to the pathogenicity of any given isolate. However, **deciphering the molecular viral and cellular determinants contributing to this process has been quite problematic and the disclosure fails to provide any illumination concerning this topic.** The problem of addressing this question was addressed by Kirchhoff *et al.* (1995), who PCR-amplified the *nef* coding region from HIV-1-infected long term nonprogressors. Although the authors identified a single patient with reproducible deletions in *nef*, the authors emphasized that these results should

be interpreted with considerable caution:

> In this report, we describe a particular HIV-1 gene defect associated with the absence of disease progression in a single patient. Our results, and those of Huang *et al.*,[17] suggest that deletions in *nef* may not be a common explanation for the absence of progression and that different factors are likely to contribute in other patients. Viral factors that could contribute include different types of mutations in a wide variety of viral genetic elements. Viral and host factors cannot be dissociated from each other, since an effective immune response is an essential feature of nonprogression. Disease outcome is likely to be determined by a delicate balance between the ability of the virus to replicate and the host's ability to mount an adequate immune response. [Emphasis added by Examiner].

Huang *et al.* (1995) also performed PCR analysis on proviral DNAs obtained from long-term survivors of HIV infection. The authors reported that:

> We found that there is no gross deletion within *nef* in the cases studied; most *nef* sequences (91.1%) obtained from 10 subjects contained a full-length and intact open reading frame. In addition, at the protein level, there were no discernible differences between the Nef consensus sequences derived from long-term survivors and those from patients with AIDS. We therefore conclude that deletion of or gross sequence abnormality within *nef* is not likely to be a common explanation for the well-being of long-term survivors of HIV-1 infection. [Emphasis added by Examiner].

Additional studies by Michael *et al.* (1995) corroborated these findings. It was reported by this group that:

> We have studied the sequence and function of the human immunodeficiency virus type 1 (HIV-1) *nef* genes from nine patients with highly divergent rates of disease progression enrolled in a longitudinal study of HIV disease ... The *nef* gene from each of these patients was amplified and cloned, and the sequence of 8 to 10 clones was determined. Only 2 of 88 (2.3%) *nef* genes recovered from these nine patients were grossly defective. Moreover, there was no relationship between the phylogeny of *nef* sequences and the corresponding rates of disease progression from these patients ... There was no correlation found between the functions of the *nef* genes from these patients and their corresponding rates of

disease progression. We conclude that the *nef* gene is not a common mediator of the rate of HIV disease progression in natural infection.

The prior art unequivocally illustrates that other viral, as well as, cellular gene products contribute to the pathogenic phenotype of any given HIV-1 isolate. Moreover, the specification asserts that changes in *nef* may contribute to disease progression, nevertheless, it is not readily manifest if each of the identified clones has been completely characterized at the molecular level and the contributions of other viral gene products and regulatory regions examined. For instance, the LTNP phenotype may result from a modification in Tat or TAR that results in lower levels of viral replication. Considering the unpredictability of the prior art, it would be premature to conclude that Nef is responsible for the LTNP phenotype, absent complete characterization of the various clones. Moreover, the findings of the prior art would preclude the skilled artisan from extending the findings of the instant application to any other HIV-1 isolate, particularly since it appears that all the clones described in the specification evolved from the same progenitor.

It was previously noted that the SBBC patients were all infected with viruses that share common genotypic/phenotypic characteristics (e.g., a deletion in the *nef*/LTR region). Applicants argue that this provides conclusive evidence that the parent virus displays reduced pathogenicity. As previously set forth, these arguments and data do not exclude the possibility that host factors and other viral factors may also contribute to the LTNP state in these individuals. Moreover, the SBBC cohort patients were all infected with the same HIV-1 isolate. The broadest claim language is not directed toward any particular isolate or patient with any particular MHC background. The prior art clearly teaches that other viral and host factors influence the pathogenicity of any

given isolate. Thus, it seems unlikely that every Nef-deficient HIV-1 virus will behave in the same manner across a genetically diverse group of people.

2) The specification fails to provide adequate guidance concerning the selection of allelic variants of *nef* that contain the requisite phenotypic properties. This concern has not been adequately addressed by applicants' responses. The SBBC patients were all infected with the **same** parental virus. Thus, **it is not readily manifest, given the teachings of Terwilliger *et al.* (1991), whether these findings can be extended to other HIV-1 isolates other than those described in the specification.** As previously stated, it was observed in the literature that **allelic variants of *nef* provide different contributions to the replicative properties of HIV-1.** Terwilliger *et al.* (1991) reported the following:

> The effects of the viral gene *nef* on human immunodeficiency virus type 1 (HIV-1) replication in culture were investigated using *nef* alleles of the HIV-1 IIIB and ELI strains. The results demonstrate significant allelic variation in the effect of *nef* on virus replication in both an established human $CD4^+$ T-cell line and primary human lymphocytes. In the context of HXB2 virus, the ELI *nef* allele but not the IIIB *nef* allele permits initiation of efficient low-multiplicity infection in primary peripheral blood mononuclear cells, including unfractionated peripheral blood lymphocytes, T cells, and monocyte/macrophages. **Within the same genetic context, the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.** Sequences in the IIIB and ELI genomes outside of *nef* also moderate the effects of *nef* on HIV-1 replication.

In view of the teachings of the prior art, the skilled artisan cannot reasonably predict which *nef* allelic variants will produce the desired LTNP phenotype.

3) The specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef*⁻ deletion variants would mount an efficacious humoral or cellular immune

response resulting in the prevention or treatment of HIV infection and the clinical sequelae leading to AIDS. A number of attendant caveats associated with the development of an efficacious HIV-1 vaccine or therapeutic were reviewed by Graham *et al.* (1995) and Haynes (1993). The rational design of an effective vaccine requires a knowledge of the pathogenesis of HIV infection and an understanding of the human correlates of protective immunity. The cruxes associated with vaccine development can be summarized as follows:

a) The correlates of human protection remain to be elucidated. Thus, it is not clear if humoral, cell-mediated, or both types of immune response will provide protection.

b) The plasticity, or quasispecies nature, of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of effective HIV-1 vaccines and therapeutics. Convincing data demonstrating that such a vaccine can neutralize diverse field isolates remains to be presented.

c) The most appropriate methods for presenting viral antigens to the immune system remains to be elucidated. Thus, it is not readily manifest which mechanisms will optimize MHC Class I- or II-dependent antigen uptake, processing, compartmentalization, and presentation.

d) The viral antigens that confer protective immunity remain to be elucidated. Thus, the skilled artisan cannot predict which immunogens (i.e., Gag, Pol, Env) should be included in a putative vaccine and the form they should take (i.e., whole viral vaccine, sub-unit).

e) The viral and cellular determinants responsible for mucosal immunity remain to be elucidated. This route of administration plays a major role in viral transmission. Any efficacious vaccine will need to generate a strong mucosal immune response, probably through the production of neutralizing secretory IgA

antibodies, to prevent the mucosal transmission of HIV-1.

f) Adequate animal models are not available for vaccine efficacy testing. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies can not be directly extrapolated to a clinical setting. Graham *et al.* (1995) specifically note (refer to pp. 1333-1334) that the **"structural differences between SIV and HIV complicate the direct translation to humans of the results of vaccine studies in the SIV-macaque system"** and that **"no animal model has been found in which an AIDS-like illness develops from a virus with the antigenic determinants of HIV-1."** It was further emphasized by Haynes (1993; refer to p. 1280) that **"In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection."**

These factors have not been adequately addressed by applicants' responses and exhibits. The reliance upon Dyer *et al.* (1999) is misdirected since the authors reported (see Abstract, p. 436) that "Proposals for the use of live attenuated human immunodeficiency virus (HIV) type 1 (HIV-1) as a vaccine candidate in humans have been based on the production afforded by attenuated simian immunodeficiency virus in the macaque model **... it is not yet known if this strategy could succeed in humans"**. Applicants appear to be suggesting that HIV-1-specific CTL responses may confer protection against the invading pathogen. However, this study (see Abstract, p. 436) noted that **"Two of seven patients had weak CTL responses, and in one recipient, no HIV-specific CTLs were detected."** Thus, nearly half of this sample population did not have strong HIV-1-specific CTL responses. This only illustrates the complexities associated with trying to ascertain which viral immunogens are capable of providing a protective or therapeutic immune response.

Moreover, the failure to elicit strong CTL responses in these individuals may be due to the replication-impaired state of the virus. Thus, **it is not readily manifest how a replication-impaired virus that replicates to such low levels would be capable of producing a robust immune response that would lead to viral inactivation and clearance.** The authors further report (see p. 441, rt. col., bridging paragraph) that "**our recent follow-up of these individuals suggests that slow disease progression may be occurring in some members with detectable viral replication. Also, declining CTLp levels in C98 suggest that CTLs may fail to adequately control viral replication in the future.**" The authors conclude (see p. 442, last paragraph) that "**We suggest that a potential vaccine candidate would require further attenuation than that in the natural SBBC viral strain ... whether such responses are capable of protecting against wild-type HIV-1 challenge remains to be determined.**" Clearly, there are a number of issues that remain to be resolved before any attenuated live HIV-1 vaccine can be utilized.

As previously set forth, the reliance upon Kent *et al.* (2001) is also misdirected. First, applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). Thus, this exhibit cannot be properly relied upon to demonstrate that the disclosure was enabled at the time of filing. Second, even if this exhibit was relied upon, it still fails to address a number of the defects previously noted by the Examiner. The claimed invention is

directed toward a replication-impaired HIV-1 construct that contains a single deletion in the *nef*/3'LTR coding/regulatory region. The teachings of Kent and colleagues are directed toward the SIV macaque model. The prior art has already clearly established that direct extrapolations vis-à-vis vaccine efficacy between humans and macaques cannot be performed due to the various genotypic/phenotypic differences between HIV and SIV, as well as, humans and macaques. Third, the construct employed by Kent *et al.* (2001) differed considerably from that currently claimed. The SIV macaque construct contained multiple deletions in both the 5' LTR and 3' *nef*/LTR as opposed to the instantly claimed construct which comprises a single *nef* mutation. This study also reported that in SIV, single deletions in the 3' *nef*/LTR overlap region actually led to sustained infection and SAIDS. Fourth, the art clearly raises a number of concerns pertaining to the utilization of replication-impaired HIV-1 constructs as vaccine vehicles (see subsequent paragraph). Thus, this publication fails to overcome the rejection.

Applicants' arguments and the evidence relied upon fail to overcome the basis for the rejection. While there has been a delayed progression toward AIDS in the SBBC cohort which appears to be attributable to the effete nature of the HIV-1 Nef-deficient isolates, nevertheless, this finding does not mean that compositions comprising these viruses will prove suitable as vaccines. First, applicants have not identified the correlates of protection in this patient sample. There has been no clear demonstration that a specific humoral, CTL, or both humoral and CTL response is required for protection. Second, it is not clear if the immune response in these patients would be effective in preventing transmission with a wildtype HIV-1 isolate with greater replicative capacity. These patients were all infected with an effete viral isolate. One reasonable explanation concerning the

delay to disease progression is simply that the virus of interest is a slow replicator. However, this does not mean that said virus is capable of inducing a protective or therapeutic immune response when used as a vaccine. Third, in the absence of a clear delineation of the correlates of protection, the skilled artisan cannot reasonably begin to ascertain if the proposed vaccine is capable of generating protective immune responses. Which immune responses are indicative of protection? Is a neutralizing antibody response generated against a specific viral antigen? What is the antibody titer and specificity that is required to achieve protection? Is a Nef-deficient viral vaccine composition capable of inducing such an immune response? Is a cytotoxic T-lymphocyte (CTL) response requried for protection? Which CTL epitopes are the target of such a response? What is the CTL titer and specificity that is required for protection? Is a the aforementioned vaccine composition capable of reproducibly generating such a response? The disclosure and applicants' response does not address any of these critical issues.

4) The prior art (Ruprecht *et al.*, 1995) raises a number of additional concerns pertaining to the safety and development of an AIDS vaccine involving *nef*-deficient viruses which are not adequately addressed by the disclosure or applicants' arguments. The findings of this article can be summarized as follows: a) **SIV mutants containing *nef*, *vpr*, and negative regulatory element (NRE) deletions replicated to high levels following oral administration to infant macaques.** All of the animals receiving this "vaccine" either developed SAIDS or display symptoms of the disease (Baba *et al.*, 1995). b) The *nef* gene product is not a direct molecular determinant for virulence. Nef appears to modulate the viral load while other determinants are responsible for the direct pathogenic properties of the virus. Accordingly, ***nef*-deficient viruses are replication-impaired, not avirulent, and can be activated (thereby**

becoming virulent) by additional host, bacterial, or viral factors. c) **Protective immune responses to SIV *nef* mutants developed quite slowly following administration of the putative vaccine.** A dilatory immune response in humans could facilitate spread of the disease through high risk behavior by encouraging a false sense of protection. d) Replication-impaired retroviruses still undergo integration into the host chromosome. This activity can potentially result in insertional mutagenesis. **Disseminated lymphoproliferative disorders were associated with the administration of an SIV *nef* "vaccine".** The authors soundly conclude (refer to page 178, final paragraph) that **"We feel that it is premature to consider *nef*-deleted viruses as candidate AIDS vaccines; they are neither safe nor sufficiently effective. The race between vaccine-virus replication and host defenses could be decided in favour of virus replication in coinfected or immunocompromised hosts."** Despite the unpredictability of the prior art and the various caveats raised by other vaccine investigators concerning the safety and efficacy of Nef-deficient viral vaccines, the applicants, nevertheless, argue that the claimed invention is fully enabled. Such a position is clearly untenable given the teachings of the art. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

35 U.S.C. § 103(a)

6. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as

> a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

8. Claims 137-152, 157, and 158 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Desrosiers (1998). This publication discloses methods for preparing Nef-deficient HIV-1 proviruses and immunogenic compositions containing said viruses, as well as, their use in the induction of immune responses in a host. This teaching does not disclose deletions in the specific region of Nef claimed by applicants. Nevertheless, this teaching clearly illustrates that deletion of the Nef coding portion results in the production of an effete virus with impaired replicative properties that still retains its immunogenicity. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare Nef-deficient HIV-1 proviruses, immunogenic compositions comprising said proviruses, and methods of administering said compositions to a host to induce

a viral-specific immune response. The immunological reagents generated from said response would be useful, inter alia, as diagnostic reagents or for the purification of viral immunogens. The precise location of the mutations in the Nef coding portion is simply a matter of routine experimentation. What is critical, is that the virus of interest not carry a functional *nef* gene. This could easily be accomplished by introducing mutations (i.e., stop codons, insertions, deletions, etc.) at any point throughout the open reading frame.

Correspondence

9. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward the following Group 1600 fax number: (703) 872-9306. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (703) 308-1122 or (703) 308-4027, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

19 October, 2003